REMARKS

This Amendment is filed concurrently with Notice of Appeal and the appropriate fee under 37 CFR §1.17(b).

Applicants request cancellation of the non-elected claims and entry of minor amendments to clarify Claim 40 and place Claim 44 in better form for consideration on appeal. Specifically, the term "active cholesteryl ester transfer protein (CETP)" in Claim 40 is replaced by "cholesteryl ester transfer protein (CETP) activity" in order to conform to the language of the rest of the claim. Claim 44 is requested to be amended to remove the term "about" from the claim, which obviates one issue of contention between the Examiner and Applicants with respect to the applicability of the sole reference relied on to reject the claims.

Reconsideration and allowance of the application are requested in view of the amendments herein and Applicants' remarks herein and as set forth in their response filed June 20, 2002.

Response to Rejections Under 35 USC § 112, first paragraph

In the Office Action of September 10, 2002, the Examiner rejected Claims 40-48, 51, and 52 under 35 USC §112, first paragraph, objecting to the scope of the claims and written description in support of the claims.

The Examiner has rejected Claims 40-48 and 51-52 as overly broad and requiring undue experimentation based on the argument set forth on pp. 2-8 of the Office Action. In particular, the Examiner asserts that the specification does not enable the claimed methods comprising administering to "any" mammal "any" non-endogenous cholesteryl ester transfer protein (CETP) in an amount effective to reduce CETP activity in the blood to a level that is less than 20% of that in the untreated mammal (Claim 40), to achieve an unexpectedly low level of circulating CETP, i.e., essentially 0 μg CETP per milliliter of blood (Claim 41), or to achieve an anti-atherogenic lipoprotein profile in the blood of the mammal wherein there is an unexpectedly high level HDL-cholesterol (Claims 42, 43) or unexpectedly low level of LDL-cholesterol (Claims 44, 45). The Examiner has further rejected as inadequately enabled Applicants' claimed methods as applied to humans (Claims 46, 48) or as employing a preferred group of whole, non-endogenous CETP molecules (Claim 47). Finally, the Examiner has rejected as not enabled Applicants' claimed methods wherein adjuvants are employed (Claims 51, 52).

For the reasons given below, Applicants submit that the claims are adequately enabled. Accordingly, Applicants respectfully traverse the rejection.

Applicants' claims are directed to methods of using a whole, non-endogenous CETP to produce a particular, measurable, anti-atherogenic condition of unexpected proportions. In particular, Applicants have discovered that administering a whole, non-endogenous CETP to a mammal will elicit production of antibodies that react with the mammal's own, endogenous CETP resulting in:

- an unexpectedly low level of circulating CETP molecules (essentially no detectable CETP per ml of blood plasma) or of CETP activity (below 20% of the activity in an untreated mammal),
- an unexpectedly high level of HDL-cholesterol (greater than 90%, and as high as 100%),
- an unexpectedly low level of LDL-cholesterol (less than 10%, and as low as, essentially, none).

Examples of achieving such measurable results according to Applicants' claimed methods are provided in the specification, using a well known rabbit model for atherosclerosis (see, Example 1 at page 16 (line 26) to page 20 (line 21) of the specification). When rabbits were put on a high cholesterol (atherogenic) diet, rabbits vaccinated with a whole recombinant human (i.e., non-endogenous) CETP had a demonstrably lower incidence of atherosclerotic lesions (see, Figure 14).

The essence of the Examiner's argument alleging a lack of enabling disclosure for Applicants' methods is that the specification does not contain an explicit disclosure of every mammalian CETP sequence and does not contain a working example of every mammalian CETP administered to every mammal. The Examiner concludes that without such disclosure, a person skilled in the art would only be able to repeat the working example of Applicants' specification, that is, to administer recombinant human CETP to rabbits and then measure antiatherosclerotic effects. According to the Examiner, this teaching could not be expanded to any other mammalian subject using any other whole non-endogenous CETP.

The Examiner's entire argument focuses on what the present specification does or does not contain and focuses not at all on the capability of persons skilled in this art. The fact that every known mammalian CETP sequence is not included in the Applicants' disclosure is of no

moment. A patent specification need not teach, and preferably omits, what is well known in the art. *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F2d 1367, 1384, 231 USPQ 81 (CAFC 1986) In the present invention, Applicants claim a *method* of using whole CETP molecules to obtain a particular lipoprotein profile in a mammalian subject. The practitioner's knowledge of specific non-endogenous CETP molecules to use in the practice of the invention is *presumed.* What Applicants have discovered is that whole, non-endogenous CETP may be administered to a mammalian subject and result in endogenous CETP levels that are unexpectedly low, endogenous HDL levels that are unexpectedly high, and endogenous LDL levels that are unexpectedly low. *What is claimed* is a method for modulating one of these levels by administering a whole, non-endogenous CETP to a subject *so as to achieve such unexpected results*, that is, it is a requirement of the claims that certain levels of CETP activity, HDL-cholesterol, or LDL-cholesterol are obtained as the result of the use of whole, non-endogenous CETP.

Applicants have demonstrated the practice of their *method* in a well known and widely used animal model that is understood and accepted by those skilled in this art. Given the applicability and acceptability of this model of mammalian cardiovascular and immune responses, Applicants submit that persons skilled in this art, seeing the operation of Applicants' method in this model, would believe that additional mammals and additional CETPs would operate in a like manner. In other words, Applicants have chosen an experimental animal that is a *model* of mammalian cardiovascular disease and immune response; and practitioners of Applicants' invention will readily apply the example of the model to other mammalian subjects in accordance with the teaching of Applicants' specification, AND such practitioners will believe that such application to other animals or humans will have comparable results as defined in Applicants' claims.

Applicants have concisely and clearly defined their method in the claims, and have defined and discussed all the claim terms in the specification and drawings. Given the level of skill in this art, Applicants submit that a person skilled in the art may repeat the working examples of Applicants' specification and, what is more, may without experimentation apply the same method to another mammal besides New Zealand White rabbits, and moreover, may without experimentation select other whole CETPs that are non-endogenous to the intended mammalian subject. Furthermore, in view of the carefully explained assays and the data

presented in the examples section of the present application, Applicants submit that a person skilled in the art can determine whether the blood level of CETP activity, HDL-cholesterol, or LDL-cholesterol in a whole-CETP-vaccinated subject has reached less than 20% or 0 μg/ml, greater than 90% or 100%, or less than 10% or "essentially none", respectively, as required by the claims.

In view of this enabling disclosure *directed to the person skilled in the art*, it is incumbent on the Examiner to explain and provide evidence in support of his contention that the person skilled in the art is incapable of knowing what is well known in the art, incapable of following the steps of Applicants' working examples, and incapable of using Applicants' model as a model for other methods encompassed by the claims.

The Examiner has pointed out that Applicants' specification does not include sequences and lists of mammalian subjects that are known in the art and necessary as starting materials as a prelude to practicing Applicant's method, but as pointed out above, that is not a requirement of 35 USC §112. The Examiner has *not* pointed out why a person skilled in the art would be unable to practice the invention as claimed, and that *is* required to make out a prima facie case of non-enablement.

For the foregoing reasons, Applicants respectfully submit that the present claims are sufficiently enabled to meet the standard required by 35 USC §112, first paragraph. Therefore, reconsideration and withdrawal of the rejection under 35 USC §112, first paragraph, are respectfully requested.

In the Office Action, page 9, the Examiner has rejected Claims 40-48 and 51-52 under 35 USC §112, first paragraph, for the reason that the specification is deemed not to reasonably convey to the person skilled in the art that the inventors were in possession of the claimed invention at the time of filing. The Examiner further directs the Applicants to the Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, ¶1, "Written Description" Requirement, as published in the Federal Register, Vol. 66, No. 4, Jan. 5, 2001, pp. 1099-1111 (hereinafter "Guidelines").

According to those Guidelines, the analysis of possession of the invention is akin to proving complete conception of an invention in an interference:

> "However, it is acknowledged that if evidence typically provided to prove a complete conception is present in the specification as filed, it would be sufficient to show possession. The Federal

> Circuit has stated '[t]he conception analysis necessarily turns on the inventor's ability to describe his invention with particularity. Until he can do so, he cannot prove possession of the complete mental picture of the invention.' (citation omitted)" (Guidelines at pp. 1101-1102.)

In discussing the General Principles to be applied by Examiners regarding compliance with the written description requirement, the Guidelines state:

> "An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as *words*, structures, figures, diagrams, and formulas that fully set forth the claimed invention. Possession may be shown in a variety of ways including *description of an actual reduction to practice*, or by showing that the invention was 'ready for patenting' such as by the disclosure of drawings or *structural chemical formulas* that show that the invention was complete, or by describing *distinguishing identifying characteristics* sufficient to show that the applicant was in possession of the claimed invention." (endnotes omitted; italics and underlining added) (Guidelines at p. 1104.)

In the present application, there is an actual reduction to practice of treatment to reduce CETP activity, raise HDL above 90% to 100%, and to lower LDL to less than 10% to essentially none, using a whole, non-endogenous CETP vaccine according to the description. See, Example 1, pp. 16-20 of the application. The whole rhuCETP used in the examples is identified using a "structural chemical formula", namely, a complete amino acid sequence (SEQ ID NO:1). The use of the CETP of SEQ ID NO:1 to lower CETP activity below 20%, to raise HDL-cholesterol above 90%, and to lower LDL-cholesterol below 10% is described in detail. See, e.g., Example 1 and Figures 8 and 9. Thus, the specification contains a demonstration of possession of the invention using the primary indicator called for by the Guidelines, namely, "description of an actual reduction to practice."

For any embodiment of the present claims not specifically exemplified in the specification, Applicants have provided a description of "distinguishing identifying characteristics" of the invention, for example, by providing: a complete description of methods of using whole CETP molecules as immunogens; the complete amino acid structures for human and rabbit CETP (SEQ ID NOs:1 and 3); and descriptions of methods for assaying the effectiveness of the vaccine (1) to cause production of endogenous CETP-binding antibodies, (2)

to cause increase in HDL-cholesterol levels, (3) to cause a decrease in free cholesterol or LDL-cholesterol levels, and (4) to cause reduction in the formation of atherosclerotic plaque on arterial surfaces. Accordingly, all of the recitations of the claims under examination have been described with such particularity that a person skilled in the art would understand that the inventors were in possession of a full conception of every feature of the invention recited in the claims.

Clearly, the invention as defined in the present claims is supported by sufficient written description in the specification, if the claims are analyzed in accordance with the Guidelines cited by the Examiner.

The Examiner appears to require a written description of the use of every possible embodiment of whole, non-endogenous CETP to reduce CETP activity, raise HDL levels, or lower LDL levels in order to satisfy the written description requirement under 35 USC §112, first paragraph. A moment's reflection will satisfy the Director that this is an impossible requirement that is neither required by 35 USC §112, first paragraph, nor sought from an analysis of the application conducted under the Guidelines. (See, also, *SRI International v. Matsushita Electric Corp. of America*, 774 Fd. 1107, 227 USPX 577 (CAFC 1985), "The law does not require that an applicant describe in his specification every conceivable and possible feature embodiment of his invention. The law recognizes that patent specifications are written for those skilled in the art, and requires only that the inventor describe the "best mode" of making and using the invention known to him at the time.")

Accordingly, for the reasons set forth above, it is respectfully submitted that the present specification provides a written description sufficient to apprise a person skilled in the art that Applicants were in full possession of their invention as of the filing date. Consequently, the written description requirement of 35 USC §112, first paragraph, has been satisfied and the rejection based on that requirement should be reconsidered and withdrawn.

Response to Rejections Under 35 USC § 102(a)

In the Office Action, Claims 40-45, 47, 51, and 52 have been rejected under 35 USC §102(a) as anticipated by PCT publication WO 96/39168 (Kwoh et al.).

With respect to WO 96/39168, the Examiner stated:

> "The 96/39168 publication teaches a method of modulating the endogenous active cholesteryl ester transfer protein (CETP) in a mammal such as a rabbit comprising administering to said

> mammal a full-length human CETP of SEQ ID NO:1 of WO 96/39168, or a [toxoid] conjugated human CETP peptide, which are non-endogenous CETP, in an amount effective to stimulate an immune response such as anti-CETP antibody wherein said antibody inhibits the function of CETP such as anti-CETP antibody wherein said antibody inhibits the function of CETP such as reducing the CETP activity below 20% of that of the untreated mammal (See abstract, Fig 2, of WO 96/39168, in particular). The reference method comprises administer[ing] to the mammal with an adjuvant . . . The reference method decreases LDL-cholesterol to less than 16% of the total cholesterol in the serum (blood plasma), which is about 10% (See Table 1, page 11, in particular). The term "about" expands the claimed 10% of the total cholesterol to read on the reference 16%. . . .
>
> "While the reference is silent that the reference method of administering to the mammal a whole non-endogenous CETP has the property of that recited in claims 41-43 and 45, the antibody directed against said non-endogenous CETP in the mammal and the functional properties of the reference antibody are the inherent property of the reference method. Therefore the claimed method appears to be the same as the prior art method. Since the Patent Office does not have the facilities for examining and comparing the method of the instant invention to those of the prior art, the burden is on applicant to show the prior art method is different from the claimed method. . . Thus, the reference teachings anticipate the claimed invention" (Office Action, pp. 11-12).

For the reasons explained below, Applicants respectfully traverse this rejection.

For anticipation under 35 USC §102 by a printed publication, that publication must teach each and every element or aspect of the claimed invention. As explained in MPEP §2131:

> **"TO ANTICIPATE A CLAIM, THE REFERENCE MUST TEACH EVERY ELEMENT OF THE CLAIM**
>
> " 'A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.' *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). 'The identical invention must be shown in as complete detail as is contained in the . . . claim.' *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989)." (emphasis in original).

Important elements of Applicants' claims are not shown in the reference.

Applicants' claimed methods recite the step of administering a whole, non-endogenous CETP to a mammal to achieve an anti-atherogenic condition characterized by levels of CETP, CETP activity, HDL-cholesterol, or LDL-cholesterol in the blood of the mammal that were specifically unknown in the art prior to Applicants' discovery. The specific recitations in the claims that CETP activity "below 20% of that of the untreated mammal" is achieved, that HDL-cholesterol comprises "greater than about 90% of the total cholesterol in the blood", and that LDL-cholesterol comprises "less than 10% of the total cholesterol in the blood", are recitations that are not shown in the cited art and are not derivable from the cited art. It could not have been communicated to a person of ordinary skill in the art from the Kwoh et al. reference that the methods presently claimed, including attainment of blood levels of CETP activty, HDL and LDL as recited, could be achieved. In other words, the cited reference does not disclose Applicants' invention *as claimed.*

Applicants note that the Examiner relies on Fig. 2 of Kwoh et al. and Table 1 of Kwoh et al. as demonstrating reduction of LDL levels using a non-endogenous CETP. However, it is emphasized that Fig. 2 and Table 1 show results from injection of rabbits with a free, linear peptide containing the carboxy terminal 11 amino acids of human CETP or a mixture of toxoid-conjugated forms of that peptide (see, Example 2, pp. 8-10 of Kwoh): The 11-amino acid peptide and the peptide/toxoid conjugates of Kwoh et al. are not the "whole, non-endogenous CETP" of the Applicants' claims. The results relied on from Fig. 2 and Table 1 are not results of immunization of a subject with whole, non-endogenous CETP. Thus, the Examiner is relying on results with apples to draw conclusions about obtaining results with oranges. Even if the results in Kwoh et al. approached the levels specifically recited in the claims, the conclusions of the Examiner would not be valid; and the same conclusions would not be drawn in the same manner by a person of ordinary skill in this art. There is no example in Kwoh et al. using a whole, non-endogenous CETP, and thus comparison of the data presented in the Kwoh et al. reference is futile.

The Examiner relies on the former claim term in Claim 44 of "*about* 10% of the total cholesterol" to expand the scope of the claim near enough to the Kwoh et al. data in Table 1 (alleged to show reduction of LDL to 16% of total cholesterol) to make the Kwoh et al. teaching citable against Applicants' claims. For the reasons set forth in the preceding paragraph, it can be seen that these data of Kwoh et al. are not applicable to Applicants' claims. However, in

addition, Applicants take exception to the interpretation of their claim term "less than about 10%" to read on "16%". The Examiner has not explained what part of Applicants' disclosure can be referred to for indication that Applicants intended a 60% margin of expansion to be made possible by including the term "about". Notwithstanding Applicants' firm belief that this strain placed on the claim terminology of Claim 44 in order to have it read on Kwoh et al. is unreasonable and unsupported, Applicants point out that this interpretation is mooted by the amendment to Claim 44 herein, which eliminates the "about" from Claim 44 and makes "less than 10%" the limit for LDL level required to fall within the scope of Applicants' claim.

In the absence of any specific teaching of Kwoh et al. with respect to levels of CETP activity, HDL levels, and LDL levels that can be achieved by vaccination with a whole, non-endogenous CETP, the Examiner argues that those results are inherently obtained by using the whole CETP molecule according to Kwoh et al.

The Examiner is guessing. It is not an inherent property of a particular whole, non-endogenous CETP that administration to a mammalian subject will unerringly result in the particular lipoprotein levels recited in the present claims. The non-endogenous CETP has to be given in an amount effective to produce the results discovered by Applicants. The fact that those discovered results could be achieved is not suggested in the reference, thus the reference provides at most only the possibility that such results might be achieved.

> "Inherency may not be established by probabilities or possibilities. The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient." *Ex parte Skinner*, 2 USPQ2d 1788 (BPAI 1986) (italics added)

The present case is not like *In re Best*, cited by the Examiner. In that case the fact that a composition heated to a certain temperature would *inherently* return to ambient temperature once the heat was removed was the property that the CCPA acknowledged must of necessity occur. Here, the results argued by the Examiner to be inherent in the use of whole, non-endogenous CETP as a vaccine are not as predictable or certain as cooling to room temperature.

For the reasons set forth above, it is seen that the Kwoh et al. publication does not teach, or suggest to a person of ordinary skill in the art, the methods, and all their recitations, defined by the present claims. Accordingly, Kwoh et al. does not anticipate the present invention *as*

claimed under 35 USC §102(a), and withdrawal of the the rejection based on Kwoh et al. is respectfully solicited.

In view of the foregoing amendments and remarks, Applicants submit that the claims of the application are in condition for allowance. Accordingly, Applicants respectfully request that the Examiner enter the amendments and pass this application to issue.

Respectfully submitted,

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Appendix A

Amendments to the Claims

(added text shown by underlining; deleted text shown by ~~strikethrough~~)

40. (amended) A method of modulating the level of endogenous~~, active~~ cholesteryl ester transfer protein (CETP) activity in a mammal comprising administering to the mammal a whole, non-endogenous CETP in an amount effective to reduce CETP activity below 20% of that of the untreated mammal.

44. (amended) A method of modulating the level of LDL-cholesterol in a mammal comprising administering to the mammal a whole, non-endogenous cholesteryl ester transfer protein in an amount effective to achieve a lipoprotein profile wherein less than ~~about~~ 10% of the total cholesterol in the blood plasma of the mammal is LDL-cholesterol.